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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RICHARD A. RUBIN, KENNETH A. GIULIANO,
ALBERT H. GOUGH, R. TERRY DUNLAY, and
BRUCE RAY CONWAY

Appeal 2010-003909
Application 10/685,737
Technology Center 1600

Before ERIC GRIMES, LORA M. GREEN, and STEPHEN WALSH,
Administrative Patent Judges.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134(a) involving claims to a machine readable storage medium. The Patent Examiner rejected the claims

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

on the ground of obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

"This invention is in the field of fluorescence-based cell and molecular biochemical assays for drug discovery." (Spec. p. 1, ll. 14-15.) According to the Specification, the invention "provides fully automated methods for measuring and analyzing cell surface receptor protein internalization during image acquisition." (*Id.* at p. 10, ll. 21-22.)

Claims 40-48, which are all the pending claims, are on appeal. Claim 40 is representative and reads as follows (emphasis added to highlight the disputed step):

40. A machine readable storage medium comprising a program containing a set of instructions for causing a cell screening system to execute procedures for measuring internalization of cell surface receptor proteins in individual cells on an array of locations which contain multiple cells, wherein the procedures comprise:

a) identifying internalized cell surface receptor proteins in multiple individual cells on the array of locations, wherein the individual cells comprise at least a first luminescent reporter molecule that labels a cell surface receptor protein of interest resulting in a labeled cell surface receptor protein, and at least a second luminescent reporter molecule that reports on cells, wherein the identifying comprises determining whether luminescent signals from the labeled cell surface receptor protein in the individual cells identified by the at least second luminescent reporter molecule meet or surpass a user-defined threshold luminescent intensity, wherein luminescent signals from the labeled cell surface receptor protein that meet or surpass the user-defined threshold luminescent intensity represent an internalized cell surface receptor protein;

b) calculating a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein

wherein the calculations provide a measure of internalization of the cell surface receptor protein in the individual cells; and

c) displaying data on the measure of internalization of the cell surface receptor protein in the individual cells.

(App. Br. 11-12.)

The Examiner rejected the claims as follows:

- claims 40-42 and 44-48 under 35 U.S.C. § 103(a) as unpatentable over Marks[2], Kallal[3], and Proffitt[4]; and
- claim 43 under 35 U.S.C. § 103(a) as unpatentable over Marks, Kallal, Proffitt, and Dunlay[5].

OBVIOUSNESS

The Issue

The Examiner's position is that the combined teachings of Marks and Kallal suggested steps a) and c) in claim 40, but not a machine readable storage medium comprising a program with instructions for executing step b). (Ans. 7.)[6] The Examiner found that Proffitt taught a computerized scanning system and algorithm able to measure relative cell numbers

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[2] US Patent No. 6,794,128 B2, issued to James D. Marks et al., Sep. 21, 2004.

[3] Lorena Kallal et al., *Visualization of Agonist-induced Sequestration and Down-regulation of a Green Fluorescent Protein-tagged β_2-Adrenergic Receptor*, 273 J. BIOL CHEM. 322-328 (1998).

[4] Robert T. Proffitt et al., *A Fluorescence Digital Image Microscopy System for Quantifying Relative Cell Numbers in Tissue Culture Plates*, 24 CYTOMETRY 204-213 (1996).

[5] US Patent No. 5,989,835, issued to R. Terry Dunlay et al., Nov. 23, 1999.

[6] Examiner's Answer mailed Sept. 14, 2009.

containing a fluorescent label. (*Id.*) Because Proffitt disclosed determining total relative fluorescence for an entire well containing cells, and Proffitt's Fig. 3 showed "the number of 'Cells per Well' that can be used to calculate the number of cells with respect to the 'Relative Fluorescence,'" it would have been obvious to determine the number of cells at a value of relative fluorescence. (*Id.*) The Examiner found that one of ordinary skill in the art would have been motivated to apply Profitt's method to the method suggested by Marks and Kallal "because Proffitt et al. teaches that this is an effective method of determining which cells are viable cells," and would have had a reasonable expectation of success in doing so. (*Id.* at 8.)

Appellants contend that the cited references "do not teach or disclose all of the claim limitations." (App. Br. 5.) Appellants point to claim 40, paragraph (b), and specifically to the part defining the method as "calculating a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein." (*Id.*) Appellants present two arguments: (1) the step b) calculation of individual cells is missing from the prior art and not suggested, and (2) it would be impossible to perform the claimed method with the prior art teachings. (*Id.* at 6-7.)

The issues with respect to this appeal are:

did the prior art teach or suggest calculating individual cells as in step b) of claim 40; and

would it have been possible to perform claim 40's method given the prior art teachings?

Findings of Fact

We adopt the Examiner's findings concerning the scope and content of the prior art, with several exceptions specifically identified in the Analysis section below.

Principles of Law

When determining whether a claim is obvious, an Examiner must make "a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995).

"Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

Analysis

(1) For their first point, Appellants argue that "the Patent Office admits that Proffitt et al teaches calculating the intensity of the 'entire well' and measures 'the relative cell number.' Thus, as admitted by the Patent Office Proffitt et al does not actually teach the stated claim limitation, as Proffitt et al does not teach measuring fluorescence from individual cell, but rather teaches a homogeneous assay, in which the fluorescence from the entire well is measured and then adjusted to get a measurement of the relative cell numbers." (Appeal Br. 6.) "[C]ontrary to the Patent Office's assertion, it would be impossible to 'measur[e] the number of cells that had internalized fluorescent protein' using the methods of Proffitt, since Proffitt teaches looking at the total fluorescence of the collection of cells in the well." (*Id.* at 6-7.)

The Examiner's pertinent findings and reasoning are at pages 5, 7 and 10-11 in the Answer. We agree that the evidence supports the findings that Marks taught measuring internalized receptors and that Proffitt suggested calculating the number of individual cells with internalized receptors. As the Examiner found, Proffitt explicitly taught that "their digital image microscopy scanning system (DIM-SCAN) can quantify total or viable cell numbers in tissue culture plates using fluorescent dyes." (Ans. 10, citing Proffitt p. 205, col. 1, ¶ 1.) That finding is a nearly verbatim quote from Proffitt. Considering Proffitt's explicit disclosure, and the Examiner's further explanation, we find Appellants' arguments to the contrary unpersuasive.

(2) For their second point, Appellants contend that, "[a]ssuming that Marks in view of Kallal teach labeling an internalizing receptor fluorescent protein . . . these labeled internalizing receptor proteins would fluoresce both when the receptor was localized to the plasma membrane and when it was internalized." (Appeal Br. 7.) This "would result in an inability to distinguish between cells in which the receptor has internalized and cells in which the receptor is localized to the surface." (*Id.*) Because, according to Appellants, "the methods of Profitt would simply look at total fluorescence from the well . . . it is not possible to calculate 'a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein.'" (*Id.*)

Claim 40's identifying step a) reads, in relevant part:

> the identifying comprises determining whether luminescent signals from the labeled cell surface receptor protein in the individual cells . . . meet or surpass a user-defined threshold

> luminescent intensity, wherein luminescent signals from the labeled cell surface receptor protein that meet or surpass the user-defined threshold luminescent intensity represent an internalized cell surface receptor protein.

(Claim 40.)

We do not find that the Answer's rejection explicitly addressed the user-defined threshold luminescent intensity, and determining whether signals exceeding the threshold represent an internalized cell surface receptor protein. Nor do we find a response to this particular argument in the Answer. The Answer cited Marks, col. 9, ll. 7-37; col. 12, l. 40 - col. 13, l. 55; col. 19, l. 57 – col. 20, l. 10; col. 46, ll. 47-48; col. 47, l. 65 – col. 48, l. 3; col. 3, ll. 17-20 and 38-40; and Fig. 9. (Ans. 5-6.) We reviewed the cited passages, including those entitled "Identification of Internalizing Polypeptides/Antibodies" and "Identification of Internalizing Receptors" (Marks, col. 12-13); and "Identification of Internalized Phage" (*id.* at cols. 19-20). We do not find an explicit disclosure of a user-defined threshold luminescent intensity, and using the threshold to discriminate between surface-bound and internalized proteins. The Examiner has not explained that a threshold and its use were implicit in Marks or Proffitt. We find that the rejection did not account for this difference between the prior art methods and the steps in Appellants' procedures. We therefore must agree with Appellants that the evidence does not support a finding that the prior art suggested distinguishing between cells in which the receptor has internalized and cells in which the receptor is localized to the surface, as claimed. Put another way, the prior art does not support finding that there would have been a reasonable expectation of success in executing a program in which

luminescent intensity above a user-defined threshold identifies cells with an internalized cell surface receptor protein.

CONCLUSIONS

Proffitt explicitly taught that its system can quantify total or viable cell numbers, thus teaching or suggesting calculating individual cells as in step b) of claim 40.

Based on the prior art teachings of record, there would not have been a reasonable expectation of success in making a storage medium comprising a program to execute all the procedures recited in claim 40.

SUMMARY

We reverse the rejection of claims 40-42 and 44-48 under 35 U.S.C. § 103(a) as unpatentable over Marks, Kallal, and Proffitt.

We reverse the rejection of claim 43 under 35 U.S.C. § 103(a) as unpatentable over Marks, Kallal, Proffitt, and Dunlay.

REVERSED

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